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EXAMINER

ROOKE, AGNES BEATA

ART UNIT

PAPER NUMBER

1653

DATE MAILED: 10/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/626,571

Applicant(s)

DRAPEAU ET AL.

Examiner

Agnes B Rooke

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 June 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-31 and 49-64 is/are pending in the application.
- 4a) Of the above claim(s) 32-48 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-31 and 49-64 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>none</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This final action is in response to the Applicant's reply filed on 06/15/2005.

Claims 1-31 and 49-64 are pending. Claims 32-48 have been canceled. New claims 58-64 have been added.

Applicant's amendments necessitated the new ground(s) of rejections presented in this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 58, and 64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In claims 1 and 64, the Applicant refers to "plasticizer" as part of the composition. However, only page 6, line 22 of the specification mentions only that plasticizers can also be added to the osteoinductive composition. The specification does not provide adequate description or examples of plasticizers or the weight percent of the plasticizer in comparison to the whole composition; where according to a dictionary a plasticizer is a compound, which increases flexibility and toughness when added to another compound.

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Further, there are many kinds of plasticizers, for example glycerol or sorbitol, but no examples are provided in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 58 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 58, the Applicant refers to a "diluent" as part of the composition, however diluent could be any liquid or solid material used to dilute or carry an active ingredient, thus an example of a diluent used in the composition should be provided.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-17, 19-23, 26-28, 31, 49-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sybert et al. (US 2002/0107570 A1) in view of Boyce et al. (U.S. 2001/0043940 A1).

Sybert et al. teach the use of demineralized bone for repair of spinal disorders. At [0051] Sybert et al. state that the mechanical strength of demineralized bone (herein after referred to as DBM) can be increased by forming chemical linkages between adjacent bone particles by exposing collagen on adjacent bone particles and forming collagen-collagen bonds. At [0042] Sybert et al. state that acid is used to demineralize bone. Sybert et al. state that chemical crosslinkages can be made using irradiation including photooxidation, UV light, microwave, and the like [0052, 0058], dehydrothermal treatment [0052, 0059], enzymatic treatment [0052] including the use of transaminase [0057], glutaraldehyde [0054], formaldehyde [0054], and dicyclohexyl carbodiimide and its derivatives [0054], polyethylene glycol dicyclic ethers [0054], and epsilon amino lysines [0053].

Boyce et al. (U.S. 2001/0043940 A1) state that the bone particles can be combined with one or more biocompatible components, such as plasticizers [0054]; where suitable plasticizers include liquid polyhydroxy compounds as glycerol, or monoacetin etc. See [0060]. (Claim 1)

It would have been obvious to a person having ordinary skill in the art to make a composition comprising crosslinked DBM and collagen because Sybert et al. state that the mechanical strength of DBM can be increased by forming chemical linkages between adjacent bone particles by exposing collagen on adjacent bone particles and forming collagen-collagen bonds, and further to improve the composition by including plasticizers as suggested by Boyce et al. (U.S. 2001/0043940 A1).

It would have been obvious to use carbodiimide (Claims 2, 49) derivatives such as N-(3-dimethylaminopropyl) N-ethylcarbodiimide hydrochloride (Claim 3) and N-hydroxysuccinimide (Claim 4) to perform the crosslinking because Sybert et al. states that carbodiimide derivatives are useful for crosslinking collagens.

It would have been obvious to use glutaraldehyde, formaldehyde/formalin, and, polyethylene glycol dicyclic ethers such as 1,4-butanediol diglycidyl ether (Claim 13) to perform the crosslinking because Sybert et al. states that these agents are useful for crosslinking collagens.

It would have been obvious to use irradiation including photooxidation, UV light, microwave, and the like (Claims 14, 15, 21, and 22) to perform the crosslinking because Sybert et al. states that these agents are useful for crosslinking collagens.

It would have been obvious to use an enzymatic treatment (Claim 16) such as the use of transaminase (Claim 17) to perform the crosslinking because Sybert et al. states that these agents are useful for crosslinking collagens.

It would have been obvious to use dehydrothermal treatment (Claim 19) to perform the crosslinking because Sybert et al. states that this method is useful for crosslinking collagens.

It would have been obvious to use epsilon amino lysines such as epsilon (gamma glutamyl) lysine (Claim 31) to perform the crosslinking because Sybert et al. states that these agents are useful for crosslinking collagens.

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It would have been obvious that all crosslinking reactions would be performed under acidic conditions because Sybert et al. teach that acid is used to demineralize bone (Claim 20).

To accelerate new bone growth and bone healing, Sybert et al. state that growth factors and cementum attachment extracts can be incorporated in, or associated with the DBM [0060, 0062]. Therefore, it would have been obvious to a person having ordinary skill in the art to make a composition comprising crosslinked DBM and collagen and growth factors and cell attachment fragments (Claim 5, 26, 50) because Sybert et al. state that the addition of growth factors will accelerate new bone growth and bone healing. These growth factors and cell attachment fragments may or may not be attached to DBM (Claims 27, 28).

To facilitate bone growth, Sybert et al. state that various types of anterior supporting structures have been employed in intervertebral spinal fusion, i.e. spacers [0082]. Therefore, it would have been obvious to a person having ordinary skill in the art to make a composition comprising crosslinked DBM and collagen and spacers (Claim 23) because Sybert et al. state that the addition of spacer will facilitate bone growth and regeneration.

Claim 53 is included in this rejection because Boyce et al. (U.S. 2001/0043940 A1) teach a composition that is compressed in a mold, where the walls of the mold can

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be coated with a slurry or a paste containing partially and/or fully demineralized and/or superficially demineralized bone particles to form an osteoimplant. See [0050].

Therefore, it would have been obvious to design a composition of Sybert et al. in a paste form that is used as a material in bone or tissue repair as suggested by Boyce et al. (Claim 53)

Claims 6, 7, 51, and 52 are being included in this rejection because Sybert et al. state at DBM is less than 1 to at least 90 weight % at [0040].

Claims 8, 9, 10, 11, 12, and 53-57 are being included in this rejection because the DBM comprises collagen and is therefore dispersed in collagen. Collagen is a scaffold protein, and the particle size of DBM is an inherent property produced by the method.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sybert et al. in view of Boyce et al. (U.S. 2002/0107570) as applied to Claims 1 and 16 above, and further in view of Simpson et al. (US 2002/0090725 A1).

The teachings of Sybert et al. are discussed above. Sybert et al. do not teach to crosslink DBM and collagen using lysyl oxidase.

Simpson et al. teach that collagens are routinely crosslinked with lysyl oxidase [0185].

Therefore, it would have been obvious for a person of ordinary skill in the art to crosslink the DBM and collagen of Sybert et al. using the lysyl oxidase of Simpson et al. because Simpson et al. teach that it is routine to cross link collagens with lysyl oxidase and Sybert et al. teach that it is beneficial to expose collagens in DBM and crosslink them to increase the mechanical strength of DBM.

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sybert et al. in view of Boyce et al. (U.S. 2002/0107570) as applied to Claim 1 above, and further in view of Fang et al. (US 5,869,527).

The teachings of Sybert et al. are discussed above. Sybert et al. do not teach to crosslink DBM and collagen by glycation or glycosylation.

Fang et al. teach that collagens are routinely crosslinked by glycation or glycosylation. Column 1, line 21-23.

Therefore, it would have been obvious for a person of ordinary skill in the art to cross link the DBM and collagen of Sybert et al. by glycation or glycosylation of Fang et al. because Fang et al. teach that it is routine to cross link collagens by glycation or glycosylation and Sybert et al. teach that it is beneficial to expose collagens in DBM and crosslink them to increase the mechanical strength of DBM.

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sybert et al. in view of Boyce et al. (U.S. 2002/0107570) as applied to Claim 1 above, and further in view of Bucala et al. (US 5,811,401).

The teachings of Sybert et al. are discussed above. Sybert et al. do not teach the DBM and collagen composition wherein the crosslinks are pentosidine crosslinks.

Bucala et al. teach that fluorescent crosslink pentosidine was isolated from human dura collagen, and that intramolecular pentosidine crosslinking can decrease solubility of structural proteins such as collagen, and trap serum proteins, such as lipoproteins to structural proteins such as collagen. See column 6, line 37-44.

Therefore, it would have been obvious for a person of ordinary skill in the art to cross link the DBM and collagen of Sybert et al. via intramolecular pentosidine crosslinks of Bucala et al. because Bucala et al. teach that intramolecular pentosidine crosslinking can decrease solubility of structural proteins such as collagen and Sybert et al. teach that it is beneficial to expose collagens in DBM and crosslink them to increase the mechanical strength of DBM.

Claims 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sybert et al. in view of Boyce et al. (U.S. 2002/0107570) as applied to Claim 1 above, and further in view of Chilkoti et al. (US 6,444,254).

The teachings of Sybert et al. are discussed above. Sybert et al. do not teach polyoxyalkyleneamine spacer or polyethylene glycol spacer in a composition of DBM and collagen.

Chilkoti et al. teach that different kinds of spacers, for example polyethylene glycol spacer that can be used in different compositions as an attachment to ligands or other structures. See column 7, line 38.

Therefore, it would have been obvious for a person of ordinary skill in the art to use spacers in a composition of DBM and collagen of Sybert et al., and particularly polyethylene glycol spacer of Chilcote et al. because Chilcote et al. teach that it is routine to use spacers such as polyethylene glycol in different compositions.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sybert et al. in view of Boyce et al. (U.S. 2002/0107570) as applied to Claim 1 above, and further in view of Boyce et al. (US 6,294,041).

The teachings of Sybert et al. are discussed above. Sybert et al. do not teach nonbioabsorbable material, such as methyl methacrylate, in a composition with DBM and collagen.

Boyce et al. teach osteoimplant composed of DBM, collagen, and methyl methacrylate as a reinforcing component in osteoimplant. Column 4, line 35.

Therefore, it would have been obvious for a person of ordinary skill in the art to make a composition of DBM and collagen of Sybert et al. with methyl methacrylate of Boyce et al. because Boyce et al. teach that it is routine to use methyl methacrylate to enforce the structure of the bone implant, composed of DBM and collagen.

Claims 58-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sybert et al. in view of Boyce et al. (U.S. 2001/0043940 A1) and taking further in view of McKay (U.S. 6,261,586 B1).

The teachings of Sybert et al. are disclosed above. Sybert et al. do not teach a plasticizer, or a composition in a paste form, or sterilization via e-beam or gamma irradiation.

Boyce et al. (U.S. 2001/0043940 A1) teach osteoimplant composed of demineralized bone particles, collagen, plasticizers, and also teach how to prepare a composition having the consistency of a paste. [0067]. The reference does not teach sterilization by gamma or e-beam irradiation.

McKay (U.S. 6,261,586 B1) teaches a bone graft substitute, were its sterilization can be provided by e-beam or gamma irradiation.

To accelerate new bone growth and bone healing, Sybert et al. state that growth factors can be incorporated in, or associated with the DBM [0060, 0062]. Therefore, it would have been obvious to a person having ordinary skill in the art to make a composition comprising crosslinked DBM and collagen and growth factors (Claim 59) because Sybert et al. state that the addition of growth factors will accelerate new bone growth and bone healing. These growth factors and cell attachment fragments may or may not be attached to DBM (Claims 27, 28).

Claims 62 is being included in this rejection because Sybert et al. state at DBM is less than 1 to at least 90 weight % at [0040].

Claim 63 is being included in this rejection because the DBM comprises collagen and is therefore dispersed in collagen. Collagen is a scaffold protein, and the particle size of DBM is an inherent property produced by the method.

Therefore, it would have been obvious to one skilled in the art to design a cross-linked composition comprising of a demineralized matrix, and collagen as described by Sybert et al., and to improve on that design by forming a product in a paste form, that contains plasticizers as taught by Boyce et al., and additionally sterilize the composition using e-beam or gamma irradiation as taught by McKay, where the method is commonly used in the art as a common procedure to sterilize implants before their insertion into a subject.

Applicant's Arguments regarding 35 U.S.C. 103 (a) Rejection

The Applicant stated that Sybert et al. fails to teach or suggest DBM in the form of DBM particles dispersed within the collagen protein in a composition as claimed, since collagen and DBM are separately identified and recited in the application and claimed; and that Sybert et al. fails to teach a composition as claimed having "DBM in the form of DBM particles dispersed within the collagen protein."

Examiner respectfully disagrees, because DBM and collagen appear in the composition together, and the term "dispersed" means to distribute as fine particles more or less evenly in the medium. Thus, in the instant invention, according to the

claims, the DBM and collagen are distributed evenly through out the composition and therefore claims 49 and 57 are anticipated by Sybert et al.

Further, the Applicant states that rejections of 1-17, 19-23, 26-28, 31, and 49-57 are not anticipated by the secondary references.

Examiner respectfully disagrees, because the secondary references positively motivate one of the ordinary skilled in the art to make the combination of features as described and claimed in the instant case.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnes Rooke whose telephone number is 571-272-2055. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-273-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

AR

A handwritten signature in black ink, appearing to read "Karen Cochrane Carlson" followed by a stylized monogram or initials.

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER